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14. ABSTRACT

Damage to the small nerve fibers that sense pain and regulate function of internal organs results in small-fiber polyneuropathy (SFPN). SFPN symptoms include unexplained chronic widespread pain (CWP) and chronic multisymptom illness (CMI) similar to Gulf War Illness. Our prior research demonstrated that SFPN is prevalent in such CWP and CMI syndromes and that it can have onset at a young age. Given these non-specific symptoms, objective testing is recommended for SFPN diagnosis. In the second year of this study Global experts participated in early rounds of a Delphi method process to determine the most reliable markers for SFPN (Case Definition) via a secure Internet site developed in year one. We also completed a retrospective study to determine if common blood tests have utility in diagnosing SFPN because some causes are treatable. We published the results in which we identified blood tests with historically good predictive value.

15. SUBJECT TERMS

Neuropathy, Gulf War Illness, chronic widespread pain, chronic multisymptom illness, small-fiber polyneuropathy, case definition

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1. INTRODUCTION:

Nerves contain motor, sensory, and autonomic axons, most of which are the small-diameter, unmyelinated C-fibers or thinly myelinated A-delta fibers that sense pain and regulate the function of internal organs and tissues. The farthest ends of these long axons easily malfunction and degenerate if their oxygen, nutrient, or energy supply is compromised, which results in small-fiber polyneuropathy (SFPN). SFPN symptoms include unexplained chronic widespread pain (CWP) and chronic multisymptom illness (CMI), including cardiovascular, gastrointestinal, microvascular, and/or disordered sweating, which contributes to heat and exercise intolerance and fatigue, similar to Gulf War Illness. Given these non-specific symptoms, objective testing is recommended for SFPN diagnosis. Our prior research suggests that SFPN is prevalent in CWP and CMI syndromes [1]. We additionally discovered SFPN that affects adolescents and adults [2]. This early-onset SFPN usually begins in adolescence or early adulthood but can linger to cause CWP and CMI for decades, like Gulf War Illness. Importantly, some causes of early-onset SFPN can be treated and even cured. Our previous preliminary data show that among 38 Gulf War veterans and 41 matched controls, 49% of veterans had objective evidence of SFPN vs. 12% of controls [3]. However, interpretation is uncertain as there is no case definition of SFPN. We propose to recruit a group of global experts and use validated methods to develop a case definition of SFPN. We will then apply this case definition in combination with clinical tests to not only look for the prevalence of SFPN among Gulf War veterans, but also to look for potentially treatable causes.

2. KEYWORDS:

Neuropathy, Gulf War Illness, chronic widespread pain, chronic multisymptom illness, small-fiber polyneuropathy, case definition

3. ACCOMPLISHMENTS:

What were the major goals of the project?

Objective/Hypothesis:
To determine the prevalence and clinical significance of undiagnosed small-fiber polyneuropathy among Gulf War veterans, and to look for potentially treatable causes of SFPN associated with Gulf War Illness.

Specific Aims:

Aim I: To develop a working Case Definition of SFPN to help physicians confirm or refute clinically suspected cases and for research use, and then to objectively diagnose the presence or absence of SFPN among Gulf War veteran using validated anatomical and physiological diagnostic tests.

Aim II: To perform blood and skin-biopsy tests for the specific treatable causes of SFPN and to compare the prevalence of identified causes in Gulf War veterans with or without SFPN to evaluate the specificity of association.

Within these Specific Aims, three tasks had elements to be performed during the second year of this study:

Task 1. Retrospective analysis and application of Delphi method to develop a Case Definition. A panel of Experts will contribute benchmark cases through which key health history parameters are used to build the Case Definition.

Task 2. Apply validated tests to veterans and diagnose SFPN (and controls in Aim II). Collect evidence pertaining to SFPN from a cohort of 80 veterans and, according to the new Case Definition, screen them for the presence or absence of SFPN in order to establish causality.

Task 3: Identify treatable causes of SFPN in Gulf War veterans. Acquire data about the causality of SFPN through tests administered to all subjects to identify abnormal results indicative of SFPN.

What was accomplished under these goals?

Aim I:

We accomplished the following under Aim I (Task 1):

1. We continued to improve the Internet site that serves as a secure platform for the Delphi process, which is also a source of information for SFPN patients and researchers. We improved functionality of the user-interface to better enable participation in the Delphi process by Global experts. The public portion of the website may be accessed at http://NeuropathyCommons.org.

2. We finalized the group of Global experts who are participating in the Delphi process to include the following 19 National and International experts:

National:

> David Herrmann, MD (University of Rochester, Rochester, NY)
> Ahmet Höke, MD, PhD (Johns Hopkins Hospital, Baltimore, MD)
> Norman Latov, MD, PhD (Weill Cornell Medical College, New York, NY)
> Glenn Lopate, MD (Washington University in St. Louis, MO)
> Anne Louise Oaklander, MD, PhD (Massachusetts General Hospital, Boston, MA)
> A. Gordon Smith, MD (University of Utah, Salt Lake City, UT)

International:

> Colin Chalk, MD, CM, FRCPC (McGill University, Montreal, Canada)
> Catharina Faber, MD, PhD (Maastricht University Medical Centre, Maastricht, Netherlands)
> Alejandra Gonzáles-Duarte, MD (Instituto Nacional de Ciencias Médicas y Nutrició Salvador Zubiran, Tlalpa, Mexico)
> Sung-Tsang Hsieh, MD, PhD, MPH (National Taiwan University Hospital, Taipei, Taiwan)
> Thierry Kuntzer, MD (Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland)
> Giuseppe Lauria, MD (Instituto Carlo Besta, Milan, Italy)
> Jean-Pascal Lefaucheur, MD, PhD (Hôpital Henri-Mondor, Public Hospitals of Paris, Paris-Est Créteil University, Créteil, France)

Xiaolei Liu, MD (Dayi Hospital of Shanxi Medical University, Taiyuan, China)
Manoj Menezes, MD (University of Sydney, Children's Hospital, Westmead, Australia)
Claudia Sommer, MD (University of Würzburg, Würzburg, Germany)
Judith Spies, MBBS, FRACP, PhD (University of Sydney, Camperdown, Australia)
Thirugnanam Umapathi, MBBS, MRCPE, FAMS (Neurology) (National Neuroscience Institute, Singapore)
Işin Ünal Çevik, MD, PhD (Hacettepe University Faculty of Medicine, Sihhiye-Ankara, Turkey)

Additionally, we finalized the group of leaders that comprise the Scientific Advisory Board to steer the Delphi process. They are:

Verne S. Caviness, Jr., MD, DPhil (Massachusetts General Hospital and Harvard Medical School, Boston, MA) *
Alain Créange, MD, PhD (Hôpital Henri Mondor, Paris Est Créteil, France) *
Peter J. Dyck, MD (Mayo Clinic, Rochester, MN)
John England, MD (Louisiana State University School of Medicine, New Orleans, Louisiana) *
Eva Feldman, MD, PhD (University of Michigan Health System, Ann Arbor, Michigan)
Riadh Gouider, MD (Razi Hospital, University of Medicine of Tunis, La Manouba, Tunisia) *
Mary M. Reilly, MD, FRCP, FRCPI (University College London, England)

* also participating as a Global expert in the Delphi process

3. Global experts have so far been asked to answer two sets of questions to begin developing the Case Definition of SFPN by applying the Delphi process. The Delphi process is characterized by sets of questions posed to experts who are given an opportunity to modify their responses in successive rounds, until consensus is achieved on the responses. The first set of questions has undergone one round of responses and is currently in the second round of responses. The second set of questions is in the first round of responses. The specific questions and results of each round are in Appendix 1.

Aim II:

While administering the initial rounds of Delphi process questions for developing the Case Definition, we completed and published a retrospective study under Aim II to identify the blood tests that may have the best predictive value for SFPN:

1. We began by focusing on the diagnostic tools remaining to be developed under Specific Aim II to help identify SFPN, specifically blood tests for markers of SFPN. To gain perspective on the relative utility of the various tests, we retrospectively examined the prevalence of abnormal blood test results among SFPN patients to see if the tests had positive predictive value for SFPN, and also considered their cost-effectiveness in light of their predictive value. The goal was to evaluate the diagnostic utility of commonly available neuropathy-related blood tests in patients with idiopathic SFPN and formulate evidence-based recommendations for testing. The methods and results of the study are described in the publication [4] which may be found at Appendix 2.

The future plan under this grant is to apply the blood tests with most utility to Gulf War Veterans who are additionally well-characterized by history, skin biopsy, dermatopathology, and autonomic function testing; and to age-matched controls, to look for the prevalence of markers of SFPN that are indicative of causality.

What opportunities for training and professional development has the project provided?

Nothing to report. This project is not intended to provide training opportunities. Nonetheless, personnel do gain additional clinical and research skills through their participation.

How were the results disseminated to communities of interest?

This project has developed an Internet framework to increase awareness within the affected community and to promote participation in this research project. The website has pages specifically dedicated to patients and their issues, providing resources for information including our research efforts. As such, it will act as an outreach and recruiting tool for Gulf War Veterans among others affected by SFPN.

We also published the study of relevant blood tests under Aim II in the *Journal of Neurology* as described above.

What do you plan to do during the next reporting period to accomplish the goals?

During the next reporting period, we will continue to engage the global experts with successive questions to arrive at a consensus Case Definition of small-fiber polyneuropathy (SFPN) via the Delphi method. This will allow us to more accurately identify verified SFPN among the research volunteers whom we will recruit and test in the coming year, to include Gulf War Veterans of diverse health histories and normal control volunteers.

4. IMPACT:

What was the impact on the development of the principal discipline(s) of the project?

A goal of this project is to generate a formal Case Definition for small-fiber polyneuropathy which is intended to guide future practice of diagnosticians. Toward that goal, we created a website with public and private Internet pages, to raise awareness of SFPN among Veterans, the general population, and health care professionals through the public pages, and to allow global experts to access the private (secure) pages to answer questions and to add case reports to arrive at a consensus Case Definition of SFPN.

What was the impact on other disciplines?

Nothing to report.

What was the impact on technology transfer?

Nothing to report.

What was the impact on society beyond science and technology?

As described above, public awareness and attitudes toward SFPN and its sufferers should be impacted by this project.

5. CHANGES/PROBLEMS:

Changes in approach and reasons for change

There have been no changes in our approach, nor are any changes anticipated.

Actual or anticipated problems or delays and actions or plans to resolve them

It has taken longer to develop the Case Definition as the responses from the Global experts in successive rounds of the Delphi process have taken longer than anticipated. We plan to increase interaction with the Global experts to accelerate consensus on the key parameters of SFPN after which we can study subjects with the identified tests. We will also begin to identify study subjects even though not all the tests may be defined yet. If necessary we are prepared to seek an extension of the period of performance to complete the study once all the test parameters are identified.

Changes that had a significant impact on expenditures

Nothing to report.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

Nothing to report.

Significant changes in use or care of human subjects

Nothing to report.

Significant changes in use or care of vertebrate animals.

Not applicable.

Significant changes in use of biohazards and/or select agents

Not applicable.

6. PRODUCTS:

Publications, conference papers, and presentations.

Journal publications

Lang M, Treister R, Oaklander AL. Diagnostic value of blood tests for occult causes of initially idiopathic small-fiber polyneuropathy. *Journal of Neurology* 2016 published online 11 October 2016. (accepted for publication 12 August 2016).

Website(s) or other Internet site(s)

The collaboration website for developing the Case Definition continues to be improved and is part of an overall laboratory website that describes small-fiber polyneuropathy, associated research, and resources. It will serve as an effective recruiting tool for Veterans and patients. The site can be accessed at http://NeuropathyCommons.org .

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name:	Anne Louise Oaklander MD, PhD
Project Role:	PI
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	2
Contribution to Project:	Dr. Oaklander oversaw design of the collaboration website and provided content to the website, finalized and contacted the International collaborators to participate in developing the case definition, developed the questions for the Delphi process, and headed the analysis and preparation of the manuscript of relevant blood tests for neuropathy.
Funding Support:	No other funding support was used to conduct the work under this award.

Name:	Max Klein PhD
Project Role:	Co-Investigator
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	3
Contribution to Project:	Dr. Klein maintained IRB and HRPO approval for this project. He also provided content to the collaboration website, advised on the Delphi Method, and analyzed Delphi process data.
Funding Support:	No other funding support was used to conduct the work under this award.

Name:	Stephanie Ortiz BS (replaced Kate O'Neil BS)
Project Role:	Clinical Studies Coordinator/Research Assistant
Researcher Identifier	

(e.g. ORCID ID):	
Nearest person month worked:	4
Contribution to Project:	Ms. Ortiz assisted with maintaining IRB (and HRPO) documentation, contributed content to the collaborative website, and advised on the design of the secure portion of the collaborative website in accordance with the Delphi Method.
Funding Support:	No other funding support was used to conduct the work under this award.

Name:	Heather Downs BS
Project Role:	Histotechnologist
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	1
Contribution to Project:	Ms. Downs contributed content to the collaborative website including detailed instructions on preparing skin biopsies, and processed administrative activities related to this study.
Funding Support:	No other funding support was used to conduct the work under this award.

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

There are no changes to report that impact personnel effort on this project.

What other organizations were involved as partners?

Nothing to report.

8. SPECIAL REPORTING REQUIREMENTS

QUAD CHARTS: A Quad Chart is provided at Appendix 3.

9. REFERENCES

1. Oaklander AL, Herzog ZD, Downs HM, Klein MM. Objective evidence that small-fiber polyneuropathy underlies some illnesses currently labeled as fibromyalgia. *Pain* 2013; 154:2310-2316.

2. Oaklander AL and Klein MM. Evidence of small-fiber polyneuropathy in unexplained, juvenile-onset, widespread pain syndromes. *Pediatrics* 2013;131:e1091-e1100.

3. Oaklander AL and Klein MM. Undiagnosed Small-Fiber Polyneuropathy: Is it a Component of Gulf War Illness? Final Technical Report GW093049, ADA613891, Sept 2014.

4. Lang M, Treister R, Oaklander AL. Diagnostic value of blood tests for occult causes of initially idiopathic small-fiber polyneuropathy. *Journal of Neurology* 2016 published online 11 October 2016.

10. ACRONYMS AND ABBREVIATIONS

AFT   Autonomic function test
CMI   Chronic multisymptom illness
CWP   Chronic widespread pain
DOD   Department of Defense
EMG   Electromyography
HRPO Human Research Protections Office
IRB   Institutional Review Board
LEP   Laser-evoked potential
MGH Massachusetts General Hospital
NCS   Nerve conduction study
PI   Principal Investigator
QST   Quantitative sensory test
SFN   Small-fiber neuropathy
SFPN Small-fiber polyneuropathy
USAMRMC US Army Medical Research and Materiel Command

APPENDIX 1. Delphi process questions and answers in each round to-date

First set of questions and responses for each round so far are as follows (All of the following are out of 23 responses per question in the first round and 6 responses, affirming or changing their responses, so far in the second round):

1. What name should be used to refer to this illness?

First round	Second round
6 SFPN (26%)	5 SFPN (22%)
16 SFN (70%)	17 SFN (74%)
1 small fiber pathology (4%)	1 small fiber pathology (4%)

2. Should we develop criteria for "definite", "probable", and "possible" cases?

First round	Second round
22 yes (96%)	(not included in the re-vote; no re-vote
1 no (4%)	necessary)

3. Should this group develop separate diagnostic criteria for clinical vs. research purposes?

First round	Second round
11 yes (48%)	10 yes (43%)
12 no (52%)	13 no (57%)

4. Which demographic data are important to collect when diagnosing small-fiber (poly)neuropathy? Check all that apply.

	First round	Second round
Age	23 (100%)	22 (96%)
Sex	23 (100%)	22 (96%)
Race	17 (74%)	16 (70%)
Ethnicity	14 (61%)	15 (65%)

5. Which diagnostic tests should this group recommend when diagnosing small-fiber (poly)neuropathy? Check all that apply.

	First round	Second round
Electromyography (EMG)	7 (30%)	5 (22%)
Nerve conduction studies (NCS)	17 (74%)	17 (74%)
Distal leg skin biopsy immunolabeled against PGP9.5	21 (91%)	22 (96%)
Quantitative sensory testing (QST)	12 (52%)	11 (48%)
Somatosensory evoked potentials (SSEP)	4 (17%)	4 (17%)
Laser evoked potentials (LEP)	5 (22%)	4 (17%)
Composite autonomic function testing (AFT)	17 (74%)	17 (74%)
--Heart rate variability during deep breathing	17 (74%) *	(In this round, the four individual AFT

--Heart rate and blood pressure responses to Valsalva	17 (74%) *	sub-tests were removed, and only "Composite AFT" was included for clarity)
--Heart rate and blood pressure responses to tilt	17 (74%) *	
--Quantitative sweat testing	17 (74%) *	

* includes responses that included either the individual sub-test or Composite AFT which includes the individual sub-tests

6. Do you wish to continue to participate?

First round	Second round
23 (100%)	23 (100%)

7. Do you have any conflicts of interest?

First round	Second round
2 yes (9%)	2 yes (9%)
21 no (91%)	21 no (91%)

7a. Please describe any conflicts of interest.

(One respondent has commercial interest in a company that processes skin biopsies; another has commercial interest in multiple sclerosis treatment and IVIg treatment laboratories)

The second set of questions and first round responses so far are as follows (All of the following are based on 15 respondents per question (as of 30 September 2016)):

"What are the most important parts of the neuro exam to include when examining a patient for possible small-fiber (poly)neuropathy?"

1. Pupils

	Important	Not important
Normality of pupil size relative for age and ambient light	6 (40%)	9 (60%)
Normality of constriction to bright light	12 (80%)	3 (20%)

2. Appearance of lower legs, feet, hands

	Important	Not important
Hair loss	7 (47%)	8 (53%)
Skin hyperperfusion (red, purple, dusky)	13 (87%)	2 (13%)
Skin hypoperfusion (white, gray)	11 (73%)	4 (27%)
Edema	10 (67%)	5 (33%)
Muscle atrophy	11 (73%)	4 (27%)
High arches	11 (73%)	4 (27%)

Hammertoes	11 (73%)	4 (27%)
Fasciculations	8 (53%)	7 (47%)
Thin, shiny atrophic skin	11 (73%)	4 (27%)
Skin excoriations or ulcers (trauma to itchy or painless areas)	13 (87%)	2 (13%)
Amputations	12 (80%)	3 (20%)

3. Motor function

	Important	Not important
Strength of great toe extension	11 (73%)	4 (27%)
Strength of finger extension	10 (67%)	5 (33%)

4. Sensory function

	Important	Not important
Joint position – great toe	13 (87%)	2 (13%)
128 Hz vibration – great toe	13 (87%)	2 (13%)
Light touch – legs, feet, toes	11 (73%)	4 (27%)
Pin sharpness– legs, feet, toes	15 (100%)	0 (0%)

5. Reflexes

	Important	Not important
Ankle jerks as compared to other reflexes such as at knees	12 (80%)	3 (20%)

APPENDIX 2. Publication of Task 2 blood test results in the *Journal of Neurology*

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ORIGINAL COMMUNICATION

Diagnostic value of blood tests for occult causes of initially idiopathic small-fiber polyneuropathy

Magdalena Lang[1] · Roi Treister[1] · Anne Louise Oaklander[1,2]

Abstract Small-fiber polyneuropathy (SFPN) causes non-specific symptoms including chronic pain, cardiovascular, gastrointestinal, and sweating complaints. Diagnosis is made from history and exam in patients with known risk factors such as diabetes, but objective test confirmation is recommended for patients without known risks. If tests confirm SFPN, and it is "initially idiopathic" (iiSFPN), screening for occult causes is indicated. This study's aim was to evaluate the 21 widely available, recommended blood tests to identify the most cost-effective ones and to learn about occult causes of iiSFPN. Records were reviewed from all 213 patients with SFPN confirmed by distal-leg skin biopsy, nerve biopsy, or autonomic-function testing in our academic center during 2013. We determined the prevalence of each abnormal blood-test result (ABTR) in the iiSFPN cohort, compared this to population averages, and measured the costs of screening subjects to obtain one ABTR. Participants were 70 % female and aged 43.0 ± 18.6 years. High erythrocyte sedimentation rate (ESR) and antinuclear antibody (ANA; ≥ 1:160 titer) were most common, each present in 28 % of subjects. The ABTR ≥3 × more prevalent in iiSFPN than in the total population were high ESR, high ANA, low C3, and Sjögren's and celiac autoantibodies. Together, these suggest the possibility of a specific association between iiSFPN and dysimmunity. ABTR identifying diabetes, prediabetes, and hypertriglyceridemia were less common in iiSFPN than in the population and thus were not associated with iiSFPN here. The six most cost-effective iiSFPN-associated blood tests—ESR, ANA, C3, autoantibodies for Sjögren's and celiac, plus thyroid-stimulating hormone—had estimated cost of $99.57/person and 45.6 % probability of obtaining one abnormal result. Angiotensin-converting enzyme was elevated in 45 %, but no patients had sarcoidosis, so this test was futile here.

Keywords Sensory polyneuropathy · Skin biopsy · Nerve biopsy · Autonomic-function testing · Immunity · Cost effectiveness

Introduction

Distal peripheral polyneuropathy is highly prevalent and often disabling. The most common complaints are sensory. Many of these patients have small-fiber-predominant polyneuropathies (SFPN), in which the unmyelinated C-fibers, A-delta fibers, and/or autonomic axons are exclusively or preferentially damaged. These thin "small-fibers" use continuous rather than saltatory conduction, and they have limited axon-transport capacity, so disruptions in energy or nutrient supply damage them preferentially. Small fibers evolved to detect and signal dangerous stimuli (transducing them as "pain" and "itch") to trigger defensive responses, and to regulate organs and tissues to optimize their function. Because of these multiple tasks, SFPN presents with varying combinations of symptoms. These include widespread chronic pain and/or itch, postural hypotension and tachycardia, nausea, constipation and/or diarrhea, and less often, urological complaints [1, 2]. Neurological examination can be unrevealing in SFPN since muscle bulk, strength, tendon reflexes, and sensations of touch, position, and vibration are usually preserved.

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Electromyography and surface nerve-conduction study (EMG/NCS) do not detect small-fiber potentials, and thus they can neither detect nor exclude SFPN. Diagnosing SFPN can be difficult unless typical symptoms arise in patients with well-recognized causes of neuropathy. In such patients, the diagnosis and its cause are inferred from the medical history, the current symptoms, and any exam findings.

In many countries, diabetes is the most common cause of polyneuropathy [3]; it causes about half of SFPN in US population-based studies [4]. The second largest group of SFPN patients, comprising 20–50 % in recent series [3–7], have "initially idiopathic" or "cryptogenic" SFPN (here abbreviated as iiSFPN). They are the focus of the current study. The reason to try to identify undetected causes in iiSFPN patients is that peripheral axons grow throughout life, so diagnosing polyneuropathy and treating its underlying causes can spur axonal regeneration, which can improve or cure patients' symptoms. In contrast, even effective palliative treatments neither restore axons nor improve their function. They also add costs and risks including opioid abuse. Therefore, neurology organizations recommend that patients with initially idiopathic sensory polyneuropathy be screened for its common occult causes [8]. In a recent study of patients with mixed distal polyneuropathies, screening led to potentially disease-modifying management changes in 25 % [9].

Previously, objective confirmation of suspected SFPN required surgical biopsy of a sensory nerve. This is invasive, expensive, and thus only rarely performed. Today, PGP9.5-immunolabeled distal-leg skin biopsies and composite autonomic-function testing (AFT) are also endorsed by neurological societies and performed more widely, identifying increasing numbers of iiSFPN patients who need screening [10–13]. Research application of skin biopsy and AFT has suggested that SFPN appears to be a common denominator in several ill-defined syndromes that include chronic widespread pain and/or symptoms of dysautonomia. For instance, half among 152 patients with postural orthostatic tachycardia syndrome (POTS) had abnormal small-fiber mediated sweat production, meeting diagnostic criteria for SFPN [14]. In addition, among 41 patients with unexplained chronic widespread pain starting in childhood (i.e., juvenile fibromyalgia), 30 % of skin biopsies, 53 % of AFT, and 2/2 nerve biopsies were diagnostic for SFPN [15]. Multiple groups have now reported that almost half of patients with fibromyalgia have objective evidence of underlying SFPN [16–23]. Given that fibromyalgia affects 2–5 % of the world's population [24], idiopathic SFPN may be far more common than appreciated, so cost-effective screening strategies are needed. Plus, analyzing large samples of verified SFPN patients, as performed here, can inform about underlying causes and mechanisms.

Blood tests are the major way of identifying occult causes of polyneuropathy. Sensory and autonomic-predominant polyneuropathies are linked to abnormal blood-test results for diabetes [3], alcohol-related liver dysfunction [25], heavy-metal toxicity [26], deficiencies of vitamins B12 (cobalamin) and folate [27, 28], high vitamin B6 [29], hypothyroidism and hyperthyroidism [30, 31], paraproteinemia [32], sarcoidosis [33], and systemic autoimmune disorders including Sjögren's syndrome (SS) [34, 35], systemic lupus erythematosus [36], and celiac [37–39]. Infectious causes include human immunodeficiency virus [40], hepatitis C [41], leprosy [42], and Lyme disease [43]. Rare genetic variants underlie some familial and sporadic cases, with a Dutch SFPN cohort having 2.3 % prevalence of SCN9A sodium-channel mutations [7].

Insufficient screening increases the risk of missing potentially curable causes but excess screening is expensive, ineffective, and can lead to more testing, risk, worry, and cost. Thus, the sensitivity, specificity of association, and cost effectiveness of recommended blood tests should be defined to guide decisions about how to screen iiSFPN patients for causality. Table 1 summarizes the sample characteristics and tests evaluated in previous screening studies of sensory-predominant polyneuropathies. The American Academy of Neurology's 2008 systematic review of screening studies only endorsed testing blood glucose, B12 and metabolites, and serum protein electrophoresis/immunofixation (SPEP/IFIX) [8]. However, these recommendations were based on studies with varying inclusion criteria. More relied on EMG/NCS than on skin biopsy, nerve biopsy, or AFT (Table 1), meaning their conclusions apply more to large-fiber than small-fiber neuropathy. Furthermore, older studies can lose relevance due to recent health trends, including earlier detection of diabetes and prediabetes. Plus, each country and region has different prevalences of specific diseases and different testing customs, so recommendations from one place cannot be globally generalized. The current study has the advantage of having the largest sample of patients with verified SFPN. It is also among the first to compare the prevalences of abnormal blood-test results (ABTR) in neuropathy patients vs. the general population, and to consider the costs of screening neuropathy patients.

Methods

Subject selection

This retrospective study was approved by the Massachusetts General Hospital (MGH) institutional review

Table 1 Study design and prevalence of abnormal blood-test results (ABTR) in prior studies and this one

First author / Location of study	Periquet Ohio/USA	Hughes London/UK	Smith Utah/USA	De Sousa New York/USA	Devigili Italy	Bednarik Czechia	Khan Ohio/USA	Peters The Netherlands	Gallagher Michigan/USA	Farhad New York/USA	Lang MA/USA
Publication Year	1999	2004	2004	2006	2008	2009	2012	2013	2013	2015	2016
Population sampled	Suspected neuropathy with foot pain, normal strength	Sensory ± motor neuropathy	Suspected sensory predominant neuropathy	Suspected small-fiber neuropathy	Suspected small-fiber neuropathy	Painful sensory neuropathy	Small-fiber ganglionopathy and axonopathy	SFPN	DSP/SFPN	Mixed, referred for idiopathic neuropathy	SFPN
Subjects with SFPN	44	Not tested	Not specified	62	67	51	175	88	52	40	195
Other samples studied	13 normal controls	50 normal controls		96 with normal skin biopsy	Other	47 Healthy controls	63 Small-fiber ganglionopathy		Various neuropathies		
Total sample size	117	100	138	158	124	131	238	88	225	284	195
Mean age (years)	57	66.9	63	56	60	58.5	55.1	56.9	63	64.0	43.0
Proportion female (%)	59	32	48	64	49	36	48	44	39	38	76
Study design	Prospective	Prospective	Prospective	Not specified	Retrospective	Prospective	Retrospective	Retrospective	Retrospective	Retrospective	Retrospective
Characterization tools											
Neuropathy symptoms	X	X	X	X	X	X	X	X	X	X	X
Medical history		X	X	X		X	X		X	X	
Family history		X	X	X		X					
Exposure to potential toxins		X		X		X					
Neurological signs on examination	X	X	X	X	X	X	X	X	X		
Quantitative sensory testing	X	X			X	X		X			
Objective diagnostic tests											
Distal leg PGP9.5 skin biopsy	X		X	X	X	X	X	X		X	X
Composite autonomic functions											X
Sural nerve biopsy	X									X	X
Electromyography/ nerve conduction	X	X	X	X	X	X	X	X	X	X	X
Laser Doppler flowmetry					X						
Laser evoked potentials					X						
Blood tests											
A1C diagnostic for diabetes	Not specified	Not specified	Not specified	Not specified	Not specified	Not specified				Not specified	5.5 %
A1C diagnostic for prediabetes	Not specified	Not specified	Not specified	Not specified	Not specified	Not specified					14.7 %

Table 1 continued

First author / Location of study	Periquet Ohio/USA	Hughes London/UK	Smith Utah/USA	De Sousa New York/USA	Devigili Italy	Bednarik Czechia	Khan Ohio/USA	Peters The Netherlands	Gallagher Michigan/USA	Farhad New York/USA	Lang MA/USA
Publication Year	1999	2004	2004	2006	2008	2009	2012	2013	2013	2015	2016
Fasting glucose for diabetes		Not specified	3.7 %		Not specified		Not specified				0.0 %
Fasting glucose for prediabetes		Not specified	7.5 %		Not specified	Not specified	Not specified				25.0 %
Glucose tolerance test for diabetes		Not specified	13 %	3 %	Not specified	Not specified	Not specified			9.2 %	0.0 %
Glucose tolerance test for prediabetes			2 %	6 %	Not specified	14.3 %	Not specified			16.2 %	
Random glucose for diabetes	0.0 %										
Thyroid stimulating hormone	0.0 %		0.0 %	2 %	Not specified	Not specified	10.3 %	Not specified	6.2 %	0.7 %	6.2 %
Thyroxine (T4)	0.0 %					Not specified	Not specified	Not specified	4.1 %		
Vitamin B12 (low)	0.0 %		2 %	6 %		Not specified	2.3 %			1.4 %	1.5 %
Methylmalonic acid	Not specified		Not specified	Not specified						Not specified	
Homocysteine	Not specified		Not specified	Not specified						Not specified	
Vitamin B1			Not specified							0.7 %	
Vitamin B6 (high)								4.5 %		2.5 %	
Vitamin B6 (low)										0.2 %	
Vitamin C	0.0 %	Not specified									
Vitamin E	0.0 %	Not specified									
Folate			0.0 %			Not specified					2.0 %
Erythrocyte sedimentation rate	Not specified		0.0 %	Not specified					22.3 %	Not specified	28.0 %
Antinuclear antibodies (ANA)	11.0 %		3 %	Not specified		Not specified			12.6 %		27.5 %
Extractable nuclear antigen antibodies	Not specified						Not specified		Not specified		
Anti-double stranded DNA				Not specified					4.5 %		
Anti-Smith antibodies				Not specified							
Ribonucleoprotein antibodies				Not specified						Not specified	
Sjogren's AB (SS-A/Ro, SS-B/La)	Not specified		0.7 %	Not specified	Not specified				Not specified	1.8 %	9.2 %
Celiac antibodies				6 %	Not specified		Not specified		12.0 %	1.4 %	3.5 %
Antineutrophil cytoplasmic AB				Not specified						Not specified	
Complement C3											11.0 %
Complement C4											15.7 %
Rheumatoid factor	Not specified			Not specified			Not specified		5.0 %	Not specified	
ANCA									12.0 %		
Cryoglobulins				Not specified			Not specified				
C-reactive protein				Not specified					17.0%	Not specified	12.6 %

Table 1 continued

First author / Location of study	Periquet Ohio/USA	Hughes London/UK	Smith Utah/USA	De Sousa New York/USA	Devigili Italy	Bednarik Czechia	Khan Ohio/USA	Peters The Netherlands	Gallagher Michigan/USA	Farhad New York/USA	Lang MA/USA
Publication Year	1999	2004	2004	2006	2008	2009	2012	2013	2013	2015	2016
Protein immunofixation	2.3 %		3 %	6 %	Not specified	Not specified	4.0 %	2.3 %		7.0 %	3.9 %
Quantitative immunoglobulins				Not specified						1.4 %	
Creatinine and/or blood urea nitrogen	0.0 %					Not specified					2.5 %
High cholesterol	28 %					70.2 %					
High triglycerides	34 %	Not specified				Not specified		1.1 %			24.7 %
Angiotensin converting enzyme				Not specified			0.0 %				44.6 %
Liver function tests	Not specified			Not specified		Not specified					14.8 %
Hydroxyurea											
Copper				Not specified		Not specified	Not specified			Not specified	
HIV	0.0 %			Not specified		Not specified	Not specified			Not specified	
Lyme disease				10 %		Not specified				0.3 %	8.7 %
Hepatitis A				Not specified		Not specified					
Hepatitis B				Not specified		Not specified				Not specified	
Hepatitis C				Not specified	Not specified	Not specified	Not specified			Not specified	1.1 %
Syphilis	Not specified					Not specified					
Myelin-associated glycoprotein antibodies	0.0 %			Not specified	Not specified	Not specified				1.4 %	
Ganglioside antibodies	Not specified	Not specified	5.5 %	Not specified			Not specified			Not specified	
Sulfatide antibodies	2.3 %			Not specified						0.30 %	
Antinerve antibodies	0.0 %	Not specified		Not specified		Not specified				Not specified	
Paraneoplastic antibodies			Not specified			Not specified				Not specified	

A1C hemoglobin A1C, *AB* antibodies, *ANCA* antineutrophil cytoplasmic antibody, *MA* Massachusetts, *HIV* human immunodeficiency virus, *PGP9.5* protein gene product 9.5, *SFPN* small-fiber polyneuropathy

board, which waived need for consent. The sample comprised all patients with objective confirmation of SFPN at MGH during 2013. Patients were not required to have had a clinical evaluation by MGH neurologists or physicians. MGH is a major referral center for peripheral nerve tests, drawing patients from throughout the northeastern US and some from across the US and other countries. Inclusion required confirmation of SFPN by any among the widely recommended objective tests—PGP9.5-immunolabeled distal-leg skin biopsy, AFT, or nerve biopsy [12, 13]—plus at least one available blood-test result. MGH performs these tests on patients referred by physicians from any office or hospital using clinically accredited facilities and approved methods and interpretations.

Data collection

Literature searches were performed to identify all neuropathy-associated medical conditions usually identified by blood tests (Table 1). This yielded the 21 blood tests studied here. The medical records of all eligible subjects were reviewed to extract the results of all tests that had been performed within 1 year before or after the objective test that diagnosed SFPN. Official reports of external tests were included, but secondary mentions in the record were excluded because they are potentially inaccurate. If the same blood test had been repeated, the result from closest to the date of the SFPN diagnostic test was used for the analysis. Test results were extracted into a spreadsheet, and the accuracy of data entry was confirmed. The dichotomization of test results as normal or abnormal (Table 2) was based on each laboratory's reference range plus the significance of values outside the reference range for neuropathy; for instance, high B12 is not associated with neuropathy, so it was coded as "normal" for this analysis. Three diabetes-related tests were studied; hemoglobin A1C (A1C), fasting plasma glucose (FPG), and the 2-h glucose value from 75-g oral glucose tolerance testing (OGTT). Normality was interpreted according to American Diabetes Association (ADA) standards. Diabetes was defined by A1C $\geq$6.5 %, fasting glucose $\geq$126 mg/dl or 2-h OGGT value $\geq$200 mg/dl. Prediabetes was defined by A1C $\geq$5.7 and <6.5 %, fasting glucose 100–126 mg/dl, or 2-h OGTT 140–199 mg/dl. Lyme disease diagnosis required immunoblot confirmation.

The presence or absence of the following SFPN-associated symptoms was extracted from medical histories: Chronic widespread pain (using the standard definition of at least 3 months of axial, plus left and right sides, plus upper and lower body pains) [44], chronic headache [15], and other somatosensory symptoms (paresthesias and hypoesthesia). The cardiovascular symptoms encoded were otherwise-unexplained dizziness, POTS, and orthostatic hypotension. Gastrointestinal symptoms comprised otherwise-unexplained chronic nausea, vomiting, diarrhea, or constipation. Otherwise-unexplained urological, sexual, and sweating complaints were also encoded. All primary results of nerve conduction and electromyography studies were recorded. In the US, test costs vary between payers, so we estimated blood-test costs using the most common metric, the Medicare reimbursement rate, which was obtained from MGH's Medicare fee schedule.

Statistical analyses

Analyses were conducted using SPSS version 19. Group characteristics were represented by means ± standard deviations. Relationships between age (dichotomized by median) and gender and the prevalence of each ABTR were analyzed by Fisher's exact tests. The prevalence of each ABTR in the study sample was calculated and compared to the prevalence of each ABTR with the best available population data from epidemiologic surveys; ideally the National Health and Nutrition Examination Survey (NHANES) or the Women's Health Study (WHS). If US population data were not available, prevalences from similar countries were used as the comparator. Because the comparator data were not prospectively obtained, we did not calculate odds ratios, and we applied a very conservative arbitrary threshold to evaluate whether a particular ABTR might be specifically associated with iiSFPN. The prevalence of an ABTR in the iiSFPN cohort had to be $\geq$ 300 % of the prevalence in the best available population prevalence for us to label the medical condition tested for as potentially associated with SFPN. The cost of screening to identify one abnormal blood-test result was calculated as 100/(ABTR % × unit test cost). Since not all patients underwent all studied tests, this estimates the minimum cost of identifying one ABTR.

Results

Sample characteristics

Two hundred thirteen patients had objective confirmation of SFPN; 166 by skin biopsy (including all 6 with nerve biopsies diagnostic for SFPN), and 47 by AFT alone. Among them, 92 % (195) had one or more blood-test results available and thus were included in the study. Only 2.5 % had known current or prior diabetes, confirming that this was a valid sample of iiSFPN patients. Patients had been referred by 29 community and hospital-based physicians of various medical specialties. Their mean age was 43.0 ± 18.6 years (range 8–81 years), 70.3 % were female, and 94.9 % were Caucasian. Among the 41

Table 2 Prevalence of abnormal test results (ABTR) in the iiSFPN cohort and in comparator populations

Test (definition of abnormal result)	Medical condition tested for	Prevalence of ABTR in sample (*n*)	Population prevalence of ABTR and source of population data
ACE (high)	Sarcoidosis [24]	44.6% (83)	Not evaluated due to positive predictive value = 0
ESR (high)	Inflammation/infection [12, 43]	28.0% (157)	5.0% in Norway [70]
ANA (≥ 1:160)	Lupus/rheumatic disease [43]	27.5% (153)	8.9% in Brazil [21]
2-hr OGTT value for prediabetes (140-149 mg/dL)	Impaired glucose tolerance (prediabetes) [5]	25.0% (8)	44.9% in US adults 45-64y from A1C , FPG, or 2-hr OGTT value NHANES [40]
Fasting plasma glucose for prediabetes (100-125 mg/dl)	Impaired fasting plasma glucose (prediabetes) [5]	25.0% (20)	44.9% in US adults 45-64y from A1C, FPG, or 2-hr OGTT value NHANES [40]
Triglycerides (high)	Hypertriglyceridemia [28]	24.7% (97)	30% NHANES [66]
Complement C4 (low)	Inflammation/vasculitis [43]	15.7% (115)	10.4% WHS [31]
Liver AST/ALT (high)	Fatty liver, alcoholism, hepatitis [73]	14.8% (162)	10% NHANES [29]
A1C for prediabetes (≥ 5.7%, <6.5)	Recent hyperglycemia (prediabetes) [5]	14.7% (109)	44.9% in US adults 45-64y from A1C, FPG, or 2-hr OGTT value [40]
C-reactive protein (high)	Injury/inflammation [25]	12.6% (95)	7.1% WHS [30]
Complement C3 (low)	Autoimmunity/vasculitis [43]	11.0% (118)	2.7% WHS [31]
AntiRo/SS-A	Sjögren's syndrome [49, 56]	9.2% (98)	0.7% WHS [31], 3.9% NHANES [54]
AntiLa/SS-B	Sjögren's syndrome [49, 56]	9.2% (98)	1.2% WHS [31], 2.4% NHANES [54]
Lyme (IgG Western Blot)	Lyme disease [25]	8.7% (104)	No data found on immunoblot positivity
A1C for diabetes (≥ 6.5%)	Recent hyperglycemia/diabetes [60]	5.5% (109)	5.8% occult DM by A1C or OGTT age 45-64 NHANES [40]
Thyroid stimulating hormone (TSH) (high)	Hyperthyroidism [1]	4.1% (145)	0.5% NHANES [27]
SPEP/IFIX	Monoclonal gammopathy [74]	3.9% (128)	3.2% for age > 50y [35]
IgA TTG antibody (high)	Celiac sprue [9]	3.5% (109)	0.5-1.0% U.S. estimate [20]
Creatinine (high)	Renal disease, Fabry [67]	2.5% (162)	No data found
Thyroid stimulating hormone (TSH) (low)	Hypothyroidism [47]	2.1% (144)	0.3% NHANES [27]
Folate (low)	Folate deficiency [33]	2.0% (49)	0.1% [44]
Vitamin B12 (low)	Vitamin B12 deficiency [60]	1.5% (135)	3.8% [52]
Hepatitis C antibodies	Hepatitis C [10]	1.1% (88)	1.6% NHANES [4]
Fasting glucose for diabetes including OGTT (≥ 126 mg/dl)	Diabetes mellitus [5]	0.0% (20)	5.8% occult DM by A1C or OGTT age 45-64 NHANES [40]
2-hr value from OGTT for diabetes (≥ 200 mg/dL)	Diabetes mellitus [5]	0.0% (8)	5.8% occult DM by A1C or OGTT age 45-64 NHANES [40]

In the "Test" column, "high" indicates that only values above the reference range were labeled as abnormal and "low" indicates that only values below the reference range were labeled as abnormal

Green shading indicates tests in which the prevalence of an ABTR in the iiSFPN cohort was ≥ 300% than the population prevalence, thus meeting this study's criteria for excess prevalence and an association; yellow shading indicates tests in which the comparison yielded uncertain results because the prevalence of ABTR in the iiSFPN cohort was greater than the population prevalence by < 300%, red shading indicates tests in which an ABTR was more common in the population than in the iiSFPN cohort, and no shading indicates that this analysis was not conducted because of missing population data, small sample size, or no positive predictive value of the abnormal test result (for ACE)

A1C hemoglobin A1C, *ACE* angiotensin converting enzyme, *ANA* antinuclear antibodies, *ALT* alanine transaminase, *AST* aspartate aminotransferase, *CRP* C-reactive protein, *ESR* erythrocyte sedimentation rate, *OGTT* 2 h oral glucose tolerance test, *IFIX* immunofixation, *SPEP* serum protein electrophoresis, *IgA antiTTG* immunoglobulin A antibodies to tissue transglutaminase

available results of EMG/NCS, 27 % identified concomitant large-fiber polyneuropathy. Regarding somatic symptoms, 86 % of the patients had chronic widespread pain and 87 % had other sensory symptoms. Regarding the studied symptoms of dysautonomia, 87 % had cardiovascular complaints, 72 % had chronic headache, 66 % had gastrointestinal symptoms, 47 % reported altered sweating, and 42 % had urological complaints.

Prevalence of abnormal blood-test results (ABTR)

Overall, 71 % of patients had $\geq$1 ABTR. The most common were high ACE in 44.6 %, high ESR in 28.0 %, and ANA $\geq$1:160 in 27.5 %. As shown in Table 2, the prevalence of abnormal test results diagnostic for diabetes ranged between 0.0 and 5.5 % for the three different blood tests analyzed. For prediabetes, between 15.0 and 25.0 % of patients had abnormalities on the tests used to identify this. Among patients with levels of complement C3 and C4, 18 had only low C4, 12 had only low C3, and both levels were low in 6. The only sex-related association was that hypertriglyceridemia was more prevalent in males ($p = 0.026$). Abnormal test results for creatinine ($p = 0.046$) and ESR ($p = 0.029$) were more common in older (above median age) than younger subjects. There were too few non-Caucasians to detect race effects.

Specificity of abnormal blood-test results

Table 2 summarizes the best available data about population prevalence of each ABTR. Abnormal results of all six tests for diabetes and prediabetes were less prevalent in the iiSFPN cohort than in the NHANES-surveyed US population, which reported 5.8 % prevalence of undiagnosed diabetes and 44.9 % total prevalence of prediabetes among US adults age 45–64 [45]. Occult diabetes and prediabetes were therefore far less common among studied iiSFPN patients than in the population.

In contrast, none among the eight blood-test markers of autoimmunity, immune dysregulation, and inflammation (high ESR, ANA $\geq$1:160, C-reactive protein, low C3, low C4, presence of anti-Ro/SS-A, anti-La/SS-B, IgA-anti-TTG) had ABTR prevalences below comparator population prevalences (Table 2). The prevalences of high ESR, high ANA, and autoantibodies diagnostic of Sjögren's and celiac were at least 300 % of comparator population prevalences, meeting this study's definition of a potentially significant association. The cohort's 27.5 % prevalence of ANA $\geq$1:160 exceeds the comparator 8.9 % Brazilian population prevalence of ANA $\geq$1:160 [46] as well as the 13.8 % US population prevalence for titer $\geq$1:80 [47]. The excess prevalences of both low and high TSH suggest associations not only with hypothyroidism but also with

thyroiditis, which is often autoimmune [48]. Together, these findings suggest that occult dysimmune/inflammatory conditions may contribute to iiSFPN in this environment.

Since we did not find the population prevalence of high ACE, the specificity of the 45 % measured prevalence of high ACE was evaluated by investigating how many patients with high ACE actually had sarcoidosis. Twenty nine iiSFPN patients with high ACE had been further specifically evaluated for sarcoidosis, with chest CT performed in 7. None among the 29 was found to have sarcoidosis, so high ACE had zero positive predictive value or evidence of specificity in the current context.

Cost effectiveness of abnormal blood-test results

As shown in Table 3, the Medicare reimbursement for each blood test ranged from $3.69 for ESR to $24.46 for Sjögren's autoantibodies. The total per-patient reimbursement for all tests was $290.63. The reimbursement for each individual test varied by less than 10-fold. But when the frequency of ABTR was factored in the cost of screening enough patients to obtain one abnormal test result ranged between $13.17 for ESR to $1441.82 for hepatitis C, a 100-fold difference.

Discussion

This study evaluated the sensitivity and cost of recommended screening tests for occult causes of iiSFPN in the northeastern US. It also considered the possibility that individual medical conditions tested for might be specifically associated with iiSFPN. This is the largest sample of patients with small-fiber axonopathy (Table 1) and one of the first to consider the costs of these blood tests. It has the limitations of retrospective studies including incomplete data. The fact that this was a single-center study conveys risk of referral bias. To reduce this, patients were not required to have been evaluated by any MGH physician, and the sample comprised patients referred for neuropathy testing by 29 physicians from diverse specialties practicing in the community and at other hospitals as well as at MGH. We also reduced referral bias by including patients who had undergone all available recommended diagnostic tests for SFPN rather than just one test. One limitation is that the demographics of the study sample did not precisely match the demographics of comparator epidemiologic surveys, meaning that the analyses about the specificity of these ABTR are imprecise. This is unavoidable in studies that use population-based controls, but the other option, case–control studies, can also be inaccurate due to much smaller samples. To compensate for this uncertainty, we used a very conservative approach of only reporting medical

Table 3 Medicare reimbursement rate for blood tests for occult causes of initially idiopathic SFPN (iiSFPN)

Blood test	More prevalent in iiSFPN	Cost per one test	Screening cost per one ABTR
ESR	YES	$3.69	$13.17
ANA	YES	$16.49	$59.96
C3	YES	$16.38	$148.91
Sjögren's antibodies (SS-A/SS-B)	YES	$24.46	$265.87
IgA antiTTG	YES	$15.62	$446.29
TSH (high or low)	YES	$22.93	$477.71
Folate	YES	$20.06	$1,003.00
Liver enzymes AST/ALT	PERHAPS	$7.06	$47.70
C-Reactive protein	PERHAPS	$7.06	$56.03
C4	PERHAPS	$16.38	$104.33
SPEP/IFIX	PERHAPS	$5.00	$128.21
Fasting glucose to detect prediabetes	NO	$5.36	$21.44
Triglycerides	NO	$7.84	$31.74
ACE	NO	$19.92	$44.66
OGTT to detect prediabetes	NO	$17.56	$70.24
A1C to detect prediabetes	NO	$13.24	$90.07
A1C to detect diabetes	NO	$13.24	$240.73
Vitamin B12	NO	$20.41	$1,360.67
Hepatitis C antibodies	NO	$15.86	$1,441.82
Lyme (Western blot)	unknown	$19.49	$224.02
Creatinine	unknown	$6.99	$279.60

Blood tests are grouped by their level of association with iiSFPN, and within those groups by screening cost per one ABTR. Fasting glucose and 2-hour OGTT to detect diabetes are not included because no patients had abnormal results thus screening costs would be infinite

conditions tested for as potentially associated with iiSFPN when prevalences of ABTR were at least three times higher in the iiSFPN cohort than in the reference population. Such large differences are unlikely to be caused merely by mismatches between the iiSFPN sample and population controls. To further compensate for potential referral bias, we also included in our specificity considerations the prevalences of individual ABTRs reported from all other available studies, as discussed below. When multiple independent investigators all reported similar ABTR prevalences, and when these all aligned either below or above population prevalences, it added weight to our impressions about possible occult medical contributors to iiSFPN. In so far as we know, this is the first such study to factor results from other cohorts into its conclusions. Another limitation is that MGH's electronic record only rarely specified if glucose measurements were 2-h values from OGTT. Since we could definitively identify only eight 2-h values, we did not include 2-h values in the specificity analyses. In addition, no population data were identified with which to evaluate specificity of the sample's prevalences of high creatinine or Lyme seropositivity.

Despite the fact that diabetes is the largest cause of SFPN in the US and in most other developed countries, the contribution of occult diabetes and prediabetes to iiSFPN remains uncertain. The 2011–2012 NHANES data indicate that the US prevalence of diabetes in adults between 45 and 65 years was 17.5 %, of which 5.8 % was undiagnosed/occult [45]. In contrast, the MGH iiSFPN cohort had a smaller 5.5 % prevalence of diabetes by A1c (Table 2) of which 2.5 % was known. Two other idiopathic neuropathy cohorts had higher rates of undiagnosed diabetes, e.g., 13 % in Utah [28] and 9.2 % in New York [5], but two others were similar, 1.7 % in Michigan [9], and 3 % in New York [49], so the overall importance of undiagnosed diabetes as a contributor to initially idiopathic SFPN remains uncertain. These prevalence differences might reflect local or demographic differences or different care patterns, so decisions on whether and how to test for undiagnosed diabetes should be made locally.

The evidence is stronger that occult prediabetes is not overrepresented among patients with initially idiopathic sensory neuropathies [50, 51]. Its prevalence here (14.7 %) and in all other US neuropathy cohorts (6.1 and 22.7 % in Michigan [6, 9], 11 % in Ohio [52], 7 and 11 % in New York [5, 49]) are far below the NHANES-based US population prevalences (e.g., 44.9 % for adults aged 45–65) [45]. A prospective Minnesota study that found no increased risk for sensory polyneuropathy among prediabetic patients versus healthy controls also supports the lack of an association [53]. The situation appears similar for hypertriglyceridemia. Although it increases the risk of diabetics developing polyneuropathy [54], prevalences in iiSFPN cohorts (24 % here, 34 % in Ohio [55]) do not exceed the 33 % population prevalence [56].

Autoimmune neuropathies are divided into those associated with systemic or multi-organ autoimmunity, and nerve-specific conditions. Systemic lupus erythematosus [36], Sjögren's [35, 57], and celiac [37–39, 58, 59] are systemic or multi-organ autoimmune conditions that are thought to include SFPN, although odds ratios have not been determined. Serologic markers for all three conditions were far more often abnormal in the MGH cohort than in the population (Table 2), further evidence linking these conditions to SFPN and suggesting that some cases of iiSFPN are immune mediated. The current study reported the highest prevalence of ANA ≥1:160 (27.5 %), with other surveys reporting 11 % [55], 12.6 % [6], and 3 % [28]. Similarly, the 9.8 % prevalence of SS autoantibodies here exceeds the 1.8 % reported from New York [5] and the 7.5 % prevalence of SS (test unspecified) from Milan [11]. The high prevalences at MGH presumably reflect this cohort's relative youth and female predominance as compared to other neuropathy cohorts. Of note, fewer than half of patients with SS-associated painful neuropathy are SS seropositive [57], thus the

actual prevalence of Sjögren's syndrome is even higher. However, the 28 % prevalence of high ESR here is comparable to the 22.3 % prevalence identified in an older, male-predominant Michigan cohort [6].

There are well-known large-fiber-specific autoimmune neuropathies affecting myelinating Schwann cells or nodes of Ranvier including Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy, and multifocal motor mononeuropathy. Autoimmune small-fiber-predominant ganglionopathies/neuronopathies are also recognized, particularly in patients with SS or cancer [60]. It is logical that small-fiber-predominant autoimmune axonopathies should also exist, and we and others have reported cases, although these conditions are not yet well-characterized [15, 61–63]. Dysimmunity may be a more common cause of neuropathy in children and young adults, since they lack most other risks [15, 62]. The slightly elevated prevalence of complement consumption seen here might signal involvement of autoantibodies, which contribute to other neuropathies in young cohorts. Other surveys did not measure complement (Table 1), but our group reported complement consumption among young patients with iiSFPN [15].

There is an established association between monoclonal gammopathies and large-fiber demyelinating polyneuropathy, but the question of an association with SFPN has not yet been examined. The 3.9 % sample prevalence of monoclonal gammopathy here and rates from most other US neuropathy studies (3.0 % in Utah [28], 4.0 % in Michigan [6], and 7.0 % in New York [5]) are slightly higher than the 3.2 % prevalence of MGUS in US adults over age 50, even though they include patients under 50 [64]. Although inconclusive, this comparison suggests a potential association. The same situation applies to elevated liver enzymes, a marker for alcoholism and hepatitis.

Regarding nutritional contributors, folate deficiency usually produces large-fiber-predominant non-demyelinating sensory axonopathy [27] and folate levels do not correlate with risk of POTS, which is a common symptom of SFPN [65]. Given the lack of evidence for an association here, plus the rarity of folate deficiency in other US neuropathy cohorts (0 %) [28] and the resulting high cost of screening (Table 2), it may not be cost-effective to screen for folate deficiency in iiSFPN in the northeastern US (Table 2). When vitamin B12 is considered, the 1.5 % prevalence of B12 deficiency here, and the 1.4 % prevalence in another New York study [5] and 2 % prevalence in Utah [28] are below population prevalence. We identified only one exception, the 6 % prevalence reported from one New York study [49]. Both low and high TSH were overrepresented in the MGH study sample by an order of magnitude as compared to population prevalence. The American Academy of Neurology and other groups do not

recommend screening neuropathy patients for hypothyroidism [6, 8], but the elevated prevalence of abnormal test results in multiple studies, the intermediate cost of TSH screening, and the immediate actionability of abnormal results, suggest that TSH be considered for inclusion in screening recommendations for the US.

We also analyzed the costs of screening (Table 3). Medicare reimbursement for the three tests recommended by the AAN [8] (glucose, B12, and SPEP/IFIX) was $42.97/person, and ≥6.8 % of the MGH cohort would have at least one ABTR. The Utah group recommended screening panel (OGTT, B12, SPEP/IFIX, and ANA) [28] incurred Medicare costs of $59.46 per patient with ≥28.6 % probability of ≥1 abnormal result in the MGH cohort. In contrast, reimbursement for the two most cost-effective and specifically SFPN-associated blood tests from the current analysis—ESR and ANA—was only $20.18/person, and these two tests alone would convey a higher 38.5 % probability of detecting at least one abnormal test result in the MGH cohort, improving sensitivity plus reducing per-patient cost. Reimbursement for the three most cost-effective and specifically associated blood tests from the current analysis—ESR, ANA, and C3—was $36.56/person with 41.0 % probability of detecting one ABTR in MGH cohort. Reimbursement for the six most cost-effective and specifically associated blood tests from the current analysis—ESR, ANA, C3, Sjögren's autoantibodies, celiac testing (IgA-anti-TTG), and TSH—was $99.57/person with 45.6 % probability of detecting one ABTR in the MGH cohort.

Another consideration pertinent to cost effectiveness is the "actionability" of each ABTR [9]. Some tests, e.g., for diabetes, malnutrition, or infectious diseases are highly actionable since they reliably diagnose curable medical conditions. The actionability of dysimmune/inflammatory markers varies. The IgA anti-TTG test for celiac has >95 % sensitivity and specificity for detecting celiac, even for the many patients with "silent celiac" who lack gastrointestinal symptoms [66], and gluten-free diets reduce celiac-induced damage and symptoms. Thus, celiac tests may be more useful than the cheaper but less-actionable ANA and ESR. However, persistently elevated ANA or ESR typically prompt additional evaluation that can uncover treatable diagnoses, including systemic lupus erythematosus. And new treatments, e.g., for hepatitis C, add new rationale for screening. In accountable-care models, it may be most cost-effective to sequentially screen iiSFPN patients beginning with high yield, specific, low cost, actionable tests and performing others later only if needed. Testing decisions should also be personalized, since risks vary with patients' locations, demographic, personal, and family histories. Familial amyloid polyneuropathy is more prevalent in specific European regions for instance. Table 1 reveals that no prior studies reported the

prevalences of abnormal results for every test they studied. Most did not include their study's definitions of normal and abnormal results for each test. More comprehensive reporting in future studies is encouraged to enable systematic review and pooling of results from multiple studies. This add power and can inform about even rare causes of initially idiopathic polyneuropathy.

Compliance with ethical standards

Conflicts of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

Ethical standards This retrospective study was approved by the Massachusetts General Hospital (MGH) institutional review board, which waived need for consent. The authors hereby declare that the research documented in the submitted manuscript has been carried out in accordance with the ethical standards.

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APPENDIX 3. Quad Chart

Characterizing Treatable Causes of Small-Fiber Polyneuropathy in Gulf War Veterans
GW130109
W81XWH-14-1-0499

PI: Anne Louise Oaklander, MD PhD   **Org:** Massachusetts General Hospital   **Award Amount:** $1,031,355

Study/Product Aim(s)
• **Aim I:** To develop a working Case Definition of SFPN, to objectively diagnose the presence or absence of SFPN among Gulf War veteran using validated anatomical and physiological diagnostic tests
• **Aim II:** To perform blood and skin-biopsy tests for the specific treatable causes of SFPN, compare the prevalence of identified causes in Gulf War veterans with or without SFPN

Approach
Task 1. Retrospective analysis and application of Delphi method to develop a Case Definition.
Task 2. Apply validated tests to veterans and diagnose SFPN (and controls).
Task 3. Identify treatable causes of SFPN in Gulf War veterans.

normal   abnormal
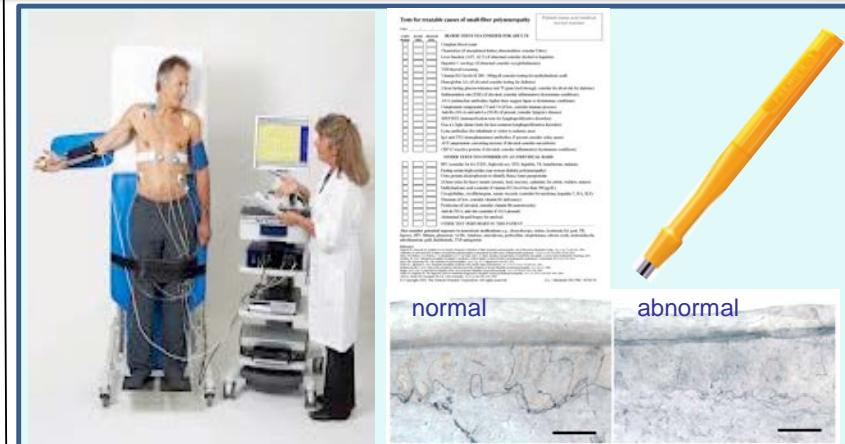
Accomplishment: Published a retrospective study under Aim II to identify the blood tests that may have the best predictive value for SFPN. Pictured are diagnostics for SFPN: autonomic function test, list of blood tests, biopsy punch, skin biopsy slides

Timeline and Cost

Activities CY	14	15	16	17
Task 1.		████ ████		
Task 2.			████ ████	
Task 3.			████ ████ ████	
Estimated Budget ($K)	**$57K**	**$344K**	**$344K**	**$287K**

Updated: 29 October 2016

Goals/Milestones (Example)
CY14 Goal – Project initiation
☑ IRB and HRPO protocol approval
CY15 Goals – Begin Delphi process, identify best tests
☑ Retrospective study of relevant blood tests
☑ Engage Global panel of experts to define SFPN diagnostics
CY16 Goal – Case definition of SFPN
☐ Experts contribute case studies, apply Delphi method
CY17 Goal – Human studies
☐ Collect detailed medical histories
☐ Apply validated tests
Comments/Challenges/Issues/Concerns
• Response time of Global experts longer than anticipated
Budget Expenditure to Date
Projected Expenditure: $686,028
Actual Expenditure: $572,446